REMARKS

The Claimed Invention and amendments above

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115 and 117-119 are pending in this application.

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115, 118 and 119 define methods of treatment using specific urea compounds.

Claim 117 defines a method for inhibiting raf-kinase in a human or mammal also using specific urea compounds. This claim has been amended to reflect effective amounts of these ureas are administered.

Information Disclosure Statement

Applicants appreciate the Examiners careful review of the information disclosure statement recently filed and the identification of the references M1 and O1 as not having a publication date. These references are foreign patents assigned to the same assignee as the present invention. The actual publication/issue date for these patents is unknown. For the purposes of this application, the publication dates for these patents can be presumed to be their filing dates, Jan 13, 2000, which has been identified on the new 1449 form submitted with the accompanying IDS and RCE.

Allowable Subject matter

Applicants acknowledge that claims 104, 115, 118 and 119 directed to treating carcinoma of the colon have been found to define allowable subject matter.

Maintained Rejections

The rejection of claims 74, 81, 87, 93, 100-103, 106-108, 110-114 and 117 under 35 U.S.C. §112, first paragraph has been maintained.

Applicants have provided additional evidence to show that the disclosure was enabling for the subject matter of these claims based on the state of the art at the time

of the invention. Additional patents have been cited in the accompanying Information disclosure statement and are discussed below.

These references show that the inhibition of raf kinase was correlated with the inhibition and treatment of a variety of tumor types and that therapeutic methods for the treatment of cancers generally were claimed in US patents. Given the state of the art, it was unnecessary to provide assays for all of the conditions to be treated.

The examiner has acknowledged the specification provides an enabling disclosure for treating carcinoma of the colon but alleges deficiencies exist in supporting the remaining claims as expressed in previous office actions. The office action dated June 29, 2006, recites the following:

"First, the instant claims cover the treatment of solid tumors carcinomas, myeloid disorders and adenomas that are known to exist and those that may be discovered in the future, for which there is no enablement provided."

"There are no known compounds of similar structure, which have been demonstrated to treat all types of the cancers recited in the claims."

"Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds."

"There is no demonstrated correlation that the tests and results apply to all disorders embraced by the instant claims."

Based on the evidence presented in previous responses and the remarks made in the final action, applicants believe these allegations have been refuted and the rejection has now been maintained based on the allegations recited in the latest office action that:

1) The state of the art is not indicative of the fact that treatments of all types of diseases encompassed by the instant claims are conventional or well known. (page 3, lines 8-10 of latest office action) and

2) There is no evidence of record that the claimed compounds are actually efficacious in treating all types of solid tumor, carcinoma, myeloid disorders, or adenoma or inhibit raf kinase generally. (page 4, lines 1-3 of latest office action).

Applicants maintain the raf kinase assays provided in the application are sufficient evidence that the compounds are actually efficacious in treating all types of

solid tumors, carcinomas, myeloid disorders, or adenomas and inhibit raf kinase generally. No evidence has been presented to the contrary.

Applicants further maintain it is not necessary to provide dedicated assays for each form of cancer claimed to enable the claimed methods. See, for example, *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not … explain every detail since he is speaking to those skilled in the art.); *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); and *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988). The MPEP also does not require dedicated assays for each treatment claimed to comply with the statute. MPEP § 2164.02 states: "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed."

In addition, Applicants are not required to demonstrate efficacy in clinical trials to satisfy the statute. See *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995). The Applicants' reliance of In re Brana is not misplaced as is alleged in the office action. Only two compounds and their salts are recited in the claims so the compounds of Brana were not "of a much narrower scope." In addition, there is no basis in the decision to interpret the holding in In re Brana as not extending to methods of treatment.

The FDA approvals of the claimed compound Nexavar for both Renal Cell Carcinoma and Hepatocellular Carcinoma and the hundreds of clinical studies with Nexavar cited earlier are consistent with the teachings within the specification that raf kinase inhibition is indicative of activity in treating solid tumors, carcinomas, myeloid disorders, or adenomas. While these events have taken place after the filing date of the application, they draw a spotlight on the absence of evidence to maintain the rejection and support Applicants' position that the raf kinase assay was sufficient for one skilled in the art to recognize the claimed compounds were effective in treating the conditions recited in claims74, 81, 87, 93, 100-103, 106-108 and 110-114. No evidence has been presented that any researcher needed to significantly deviate from the teachings within this application to use Nexavar or that the assays disclosed were ineffective in identifying active compounds.

Applicants have demonstrated through state of the art references (Monia, Kolch, Daum et al. and Fridman et al) that a correlation between the inhibition of raf kinase with the inhibition of the growth of a variety of solid tumor types (Monia et al.), the blocking cell proliferation (Kolch et al.) and the reversion of transformed cells to the normal growth phenotype (Daum et al., Fridman et al) was known to exist at the time of the invention.

These state of the art references (Monia, Kolch, Daum et al. and Fridman et al) provide no question that raf kinase inhibition was associated with the treatment of various cancers. Applicants have presented additional evidence, in the form of claims within US patents that are prior art to the present invention which recite general methods for treating cancer with raf kinase inhibitors. In view of this evidence, the state of the art at the time of the invention was such that raf kinase inhibition was known to be an activity effective for the treatment of a number of diseases including those encompassed by the instant claims.

Monia et al . US 6,090,626

This patent was filed on August 28, 1998 and is prior art to the present invention. It claims methods for inhibiting raf kinase and methods of inhibiting hyperproliferation of cells, as shown below.

6. A method of inhibiting the expression of human c-raf comprising contacting tissues or cells which express human c-raf with an antisense oligonucleotide of claim 1 under conditions wherein the antisense oligonucleotide inhibits human c-raf expression.

7. A method of inhibiting hyperproliferation of cells comprising contacting hyperproliferating cells with an antisense oligonucleotide of claim 1 under conditions wherein the antisense oligonucleotide inhibits human c-raf expression.

14. A method of inhibiting the expression of human c-raf comprising contacting tissues or cells which express human c-raf with an antisense oligonucleotide of claim 8 under conditions wherein the antisense oligonucleotide inhibits human c-raf expression.

15. A method of inhibiting hyperproliferation of cells comprising contacting hyperproliferating cells with an antisense oligonucleotide of claim 8 under conditions wherein the antisense oligonucleotide inhibits human c-raf expression.

29. A method of inhibiting the expression of human A-raf comprising contacting tissues or cells which express human A-raf with an antisense oligonucleotide of claim 23 under conditions wherein the antisense oligonucleotide inhibits human A-raf expression.

30. A method of inhibiting hyperproliferation of cells comprising contacting hyperproliferating cells with an antisense oligonucleotide of claim 23 under conditions wherein the antisense oligonucleotide inhibits human A-raf expression.

US Patent 5,994,412 Lee , et al.

This patent was filed on July 2, 1998 and is prior art to this invention. It claims compounds which are raf inhibitors and methods for treating cancer in general with these inhibitors, as shown below.

3. A method of treating cancer in a mammalian patient in need of such treatment comprising admininstering to said patient an anti-cancer effective amount of a compound in accordance with claim 1.

4. A method in accordance with claim 3 wherein the cancer is a Raf mediated cancer.

US Patent 5,767,075 to Avruch, et al.

The application which resulted in this patent was filed June 2, 1995 and claims general methods for inhibiting raf in an animal using a peptide, as shown below.

1. A method of inhibiting a direct interaction of Ras with Raf in an animal, said method comprising administering an effective amount of a Ras-binding peptide to said animal, wherein

(a) said Ras-binding peptide has an amino acid sequence with 80-100%

identity to SEQ ID NO: 6, 7, 9, 10, or 11; and

(b) said Ras-binding peptide inhibits a direct interaction of Ras with Raf.

US Patent 5,717,100 to Selnick, et al.

This patent issued in 1998 and claims general methods of treating cancers that respond to the inhibition of raf kinase, as shown below.

28. A method of treating cancers that respond to inhibition to RAF kinase which comprises administering to a mammalian patient in need of such treatment a compound in accordance with claim 1 in an amount which is effective to treat said cancers.

29. A method of treating a cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound as described in claim 1 in an amount which is effective to treat said cytokine mediated disease.

Applicants maintain that the express disclosure within the specification is sufficient to enable all of the claims herein. Based on the teachings within the art of the broad spectrum of activity of raf kinase inhibitors, one skilled in the art would recognize that the compounds recited in the claims herein having raf kinase activity would be effective in treating the diseases claimed.

Claims 87, 93, 100-103,108, 109 and 111-114

These claims specify the treatment of specific cancers. The reasons set forth on page 3, lines 8-10 and page 4, lines 1-3, (repeated above) do not apply to these claims. Raf kinase inhibition has been expressly associated with the treatment of the conditions identified in claims 87, 93, 100-103,108, 109 and 111-114 by prior art references such as Monia. Therefore, these claims are clearly enabled by the specification and the rejection of these claims under 35 USC §112 first paragraph, should be withdrawn.

Claim 117

Claim 117 is directed to a method of inhibiting raf-kinase in a human or other mammal with one of the two compounds listed. The specification provides sufficient guidance to prepare the two urea compounds and also provides sufficient guidance on how to prepare and administer compositions with these compounds, including dosages. The assays disclosed in the application clearly show that the free base of these compounds, compounds 42 and 43, inhibit raf kinase, so there is no question claim 117 is enabled.

The examiner has not identified any element of the claim for which the disclosure is allegedly deficient and has not identified any claim term, which is allegedly indefinite. Instead, the examiner alleges it is a "reach through" claim. Claim 117 is directed to inhibiting raf kinase in a patient in need thereof. This claim does not exclude those skilled in the art from subject matter beyond the scope of their invention. Therefore, claim 117 is not a reach through claim. US Patent 6677368 has similar claims (claims 3, 4 and 7 shown below) which recite a broader scope of compounds, as shown below.

> 3. A method of modulating the catalytic activity of a protein kinase comprising contacting said protein kinase with a compound of claim 1, or a pharmaceutically acceptable salt thereof.
>
> 4. The method of claim 3, wherein said protein kinase is selected from the group consisting of a receptor tyrosine kinase, a non-receptor tyrosine kinase and a serine-threonine kinase.
>
> 7. The method of claim 4, wherein said serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2, Raf, NEK and BUB 1.

In that there is no evidence claims 117 fails to meet the requirements of the statute, the rejection of claim 117 should be withdrawn.

For the reasons indicated above, Applicants maintain that they have provided more than adequate guidance and examples to enable the claimed invention and

submit all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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